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P.D.

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/487,558 01/19/00 BUSBY

R 109272.130

HM22/0522

EXAMINER

Wayne A. Keown, Ph.D.  
Hale and Dorr LLP  
60 State Street  
Boston MA 02109

DAVIS, K

ART UNIT	PAPER NUMBER
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1636

DATE MAILED:

05/22/01

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

<b>Offic Action Summary</b>	Application No.	Applicant(s)
	09/487,558	BUSBY ET AL.
	Examin r	Art Unit
	Katharine F. Davis	1636

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 14 March 2001.

2a) This action is FINAL.                    2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disp sition of Claims

4) Claim(s) 1-103 is/are pending in the application.

4a) Of the above claim(s) 29-101 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-28, 102 and 103 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

15) Notice of References Cited (PTO-892)

16) Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.

18) Interview Summary (PTO-413) Paper No(s). 8 .

19) Notice of Informal Patent Application (PTO-152)

20) Other: *Notice To Comply* .

## **DETAILED ACTION**

This Office Action is in response to the application filed on January 19, 2000 and to the Response to Restriction Requirement filed March 14, 2001. Claims 1-103 are pending in the instant application.

### ***Election/Restrictions***

In the March 13, 2001 telephone interview with Applicants' representative it was agreed upon to rejoin Groups I and II into a single group for prosecution in the instant application. The rejoining of Groups I and II is considered proper because both groups are drawn to a method of improving the production of a secondary metabolite in a fungus. The claims of Group I are drawn to improving the production of a secondary metabolite by improving the yield of the secondary metabolite and the claims of Group II drawn to improving the production of a secondary metabolite by improving the productivity of the secondary metabolite. An improvement in the productivity of a secondary metabolite is a means to increase the yield of a secondary metabolite; thus the Groups are properly rejoined.

Applicants' election without traverse of Groups I and II (hereafter known as Group I) in Paper No. 7 is acknowledged. Claims 29-101 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

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currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

***Priority***

It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 60/160,587, and filed October 20, 1999. A reference to the prior application must be inserted as the first sentence of the specification of this application if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a).

***Specification***

The specification contains nucleotide and/or amino acid sequences (see pages 67, 68, 73 and 76-79) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures. Applicant must provide a paper copy and a computer readable copy of the Sequence Listing and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37

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CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). A full response to this Office action must include a complete response to the requirement for a new Sequence Listing.

***Claim Objections***

Claims 102 and 103 are objected to because of the following informalities: they are dependent upon non-elected claims and they are also objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim (claims 14 and 28). See MPEP § 608.01(n). Appropriate corrections are required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-28, 102 and 103 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph “Written Description” Requirement

published in the Federal Register (Volume 64, Number 244, Pages 71427-71440). Claims 1-28, 102 and 103 are drawn to methods to improve the production of a secondary metabolite by a fungus (said methods comprising modulation of a gene involved in regulation of the secondary metabolite production), a fungus which is genetically modified by said methods and also a method for making a secondary metabolite comprising culturing said genetically modified fungus. These are genus claims encompassing methods for the modulation of any gene (other than those genes encoding biosynthetic enzymes for the secondary metabolite production or those genes negated in claims '1 and 15) in any fungus to improve the production of any secondary metabolite. The instant specification discloses four examples of said methods: the overexpression of the cAMP-dependent protein kinase *TPK2* from *Saccharomyces cerevisiae* in *Aspergillus terreus* to improve the production of lovastatin by decreasing the synthesis of other non-desired metabolites, expression of the transporter genes *PUMP1* and *PUMP2* from *Aspergillus terreus* in *Saccharomyces cerevisiae* to confer resistance to toxic levels of a secondary metabolite to allow increased culture times to obtain improved metabolite production, expression of a mutated form of the G-protein (G-proteins are involved in cell wall formation) *RHO1* from *Saccharomyces cerevisiae* in *Aspergillus terreus*, *Aspergillus nidulans* and *Penicillium chrysogenum* to allow conditional cell lysis at the end of fermentation cycles for facilitated purification of the metabolite produced, and expression of a mutated form of the G-protein *Rsr1* from *Saccharomyces cerevisiae* in *Aspergillus terreus*, *Aspergillus nidulans* and *Penicillium chrysogenum* to produce a morphological phenotype (for example, decreased filament length) that is advantageous for improved production of secondary metabolites in the bioreactor environment. The instant specification does not describe or identify how to modulate

other genes in other fungal strains to improve production of a secondary metabolite.

Furthermore, the instant specification does not teach any other specific examples of the types of modulations as recited in claims 2-13 and/or 16-27 (for example, dominant neomorphic mutations). The disclosure of the five genes (with methods for their modulation to improve secondary metabolite production) is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision the complete sequence of any other gene (or envision a method for its modulation in an appropriate fungal host cell) based on the disclosed examples. There is no description of a representative number of species by partial structure and a function which correlates with structure as each of the five disclosed genes (and the methods for their modulation) are unrelated and cannot be assumed to operate similarly in any other fungal species. Additionally, there is no description of a representative number of species of modulations and/or modulators (as they are recited in claims 2-13 and/or 16-27; for example dominant negative, dominant positive, etc.) by partial structure and a function which correlates with structure as the instant specification provides only what is meant by these terms without teaching specific examples. Therefore, the specification does not describe the claimed methods to improve production of a secondary metabolite in a fungus in such full, clear, concise and exact terms so as to indicate that applicants had possession of these methods at the time of filing of the present application. Thus, the written description requirement has not been satisfied.

Claims 1-28, 102 and 103 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the four examples (described above in the Written Description section), does not reasonably provide enablement for methods for the modulation of any gene in any fungus to improve the production of any secondary metabolite. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are broad in they encompass any method to modulate any gene in any fungus using any modulator to improve the production of any secondary metabolite.

The nature of the invention is a method to improve the production of a secondary metabolite in a fungus.

An analysis of the prior art indicates that there is little art on improving the production of a secondary metabolite in a fungus by genetic modulation of genes other than the biosynthetic pathway genes.

The relative skill of those in the art of fermentation and the production of commercially important secondary metabolites in fungi is high.

The area of the invention is unpredictable. As discussed above, there is a lack of teachings on genes to be targeted or on how to modulate these genes in order to use them to

improve the production of a secondary metabolite. Thus, the ability to make and use such modulated genes to improve the production of a secondary metabolite in a fungus is unknown.

The instant specification provides little direction or guidance to support the claimed invention. While the instant specification discloses the four examples (described above in the Written Description section) it does not describe or identify how to modulate other genes in other fungal strains to improve production of a secondary metabolite. A “laundry list” of genes that may be modulated does not constitute an enabling disclosure of how to modulate the genes on the list to improve the production of a secondary metabolite in any fungal host cell. In order to practice the invention one of skill in the art would need to determine both which genes should be modified and the appropriate fungal host in which to carry out the modification. One of skill in the art would then need to determine how to identify and/or design modulators. The instant specification is silent with regard to these issues.

The working examples disclosed in the instant specification show only the use of the five genes (described above in the Written Description section) and no other genes or methods for their modulation to improve secondary metabolite production in a fungus.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the instant specification to teach how to modulate any gene in any fungus to improve the production of any secondary metabolite. In order to determine how to use the claimed methods to improve the production of a secondary metabolite in a fungus one of skill in the art would have to identify all possible genes in all types of fungi that are involved in regulation of secondary metabolite production and how to modulate them to improve production of a secondary metabolite. Since neither the prior art nor the present

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specification provides the answers to these questions it would require a large quantity of trial and error experimentation by the skilled artisan to answer these questions and successfully make and use the claimed invention.

Based on the broad scope of the claims, the nature of the invention, the skill of those in the art, the unpredictability of the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to make and use the claimed methods for the improvement of secondary metabolite production in a fungus.

### *Conclusion*

Claims 1-28, 102 and 103 are rejected. Claims 1-28, 102 and 103 are free of the prior art. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katharine F. Davis whose telephone number is (703) 605-1195. The examiner can normally be reached on Monday-Friday (8:30am-5:00pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Schwartzman can be reached on (703) 308-7307. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications. Any inquiry concerning the formalities of this application should be directed to Patent Analyst Dianiece Jacobs whose telephone number is (703) 305-

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3388. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Katharine F. Davis

May 21, 2001



ROBERT A. SCHWARTZMAN  
PRIMARY EXAMINER

<b>Interview Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	09/487,558	BUSBY ET AL.
	Examiner Katharine F. Davis	Art Unit 1636

All participants (applicant, applicant's representative, PTO personnel):

(1) Katharine F. Davis. (3) \_\_\_\_\_.  
 (2) Wayne A. Keown. (4) \_\_\_\_\_.

Date of Interview: 13 March 2001.

Type: a) Telephonic b) Video Conference  
 c) Personal [copy given to: 1) applicant 2) applicant's representative]

Exhibit shown or demonstration conducted: d) Yes e) No.  
 If Yes, brief description:

Claim(s) discussed: 1-28, 102 & 103.

Identification of prior art discussed: *no prior art was discussed*.

Agreement with respect to the claims f) was reached. g) was not reached. h) N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: discussed the restriction requirement mailed December 15, 2000 and agreed to the re-joining of Groups I and II (Group I; claims 1-14, 102 & 103, Group II; claims 15-28, 102 & 103) because both groups are directed to improving the production of a secondary metabolite in fungi.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

i) It is not necessary for applicant to provide a separate record of the substance of the interview(if box is checked).

Unless the paragraph above has been checked, THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an attachment to a signed Office action.

\_\_\_\_\_  
 Examiner's signature, if required

## Summary of Record of Interview Requirements

### **Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record**

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

### **Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews Paragraph (b)**

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

### **37 CFR §1.2 Business to be transacted in writing.**

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check the appropriate box at the bottom of the Form which informs the applicant that the submission of a separate record of the substance of the interview as a supplement to the Form is not required.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner.  
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

### **Examiner to Check for Accuracy**

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

Applicant must file the items indicated below within the time period set by the Office communication to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- 7. Other: \_\_\_\_\_

**Applicant Must Provide:**

- An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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